REMARKS

Claims 1-10, 14-18, 25-29, 32-37, 41-44, 46, and 48-63 are pending and have been rejected. Claims 1-8, 10-13, 16-24, 30, 31, 38-40, 45, 47, 49-51, 53, 54, 56, 58, 62 and 63 are canceled. Claims 9, 14, 15, 25-29, 32-27, 41-44, 46, 48, 52, 55, 57, and 59-61 remain in the case.

The independent claims have been amended to recite that the animal is a cat or dog, and the B-cell disorder is a lymphoma or leukemia. These features were cited in dependent claims 54, 55 and 58. No new issue requiring further search is therefore required in view of the amendments proposed herein, which reduce the number of claims and further focus the issues in this case. Entry of the claim amendments is respectfully requested.

Claims 1-3, 5-10,14-18,25-29,32-37,41-44,46,48 and 52-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brozek, C. M. *et al.* (*J Clin Lab Immunol.* 31 (3): 105-9, March 1990), and further in view of Kvalheim (Journal of the National Cancer Institute 80(16): 1322-1325, October 19,1988), Leskovar (U.S. Patent Application Publication number 2002/0094542, effective filing date May 3, 1999), Rybak *et al.* (*Proc. Nat. Acad. Sci. USA* 89: 3165-3169, April 1992), Hanna *et al.* (U.S. Patent Application Publication number 2001/0018041, filed April 16, 2001) and Halliwell (*J. Am. Vet. Med. Assoc.* 181(10): 1088-96, Nov. 15, 1982).

The primary reference is Brozek *et al.* As previously noted, Brozek does not teach that anti-HLA-DR antibodies are effective to treat a B-cell disorder in animals. The first sentence of Brozek says that anti-MHC class II antibodies have been used to treat autoimmune disease. "Anti-MHC class II antibodies" encompass more than anti-HLA-DR antibodies; it encompasses anti-DR, anti-DQ and anti-DP antibodies. The rest of the Brozek abstract highlights that there are differences between anti-DR and anti-DQ antibodies with respect to RA in humans. Given this teaching, it cannot be taken from Brozek that any anti-MHC class II antibody will be effective to treat a B-cell disorder in animals. A statement about anti-MHC class II in animals does not equate to a teaching of anti-DR in animals, since Brozek makes it clear that members of the genus of anti-MHC class II antibodies behave differently in humans. Furthermore, there is nothing in the Brozek abstract to teach the skilled artisan that anti-DR antibodies in particular (as opposed to other anti-MHC class II antibodies) might be useful in treating a B-cell disorder in animals.

The examiner finds this argument not to be persuasive, arguing that "Brozek clearly teaches successful treatment with several monoclonal anti-DR antibodies to specifically inhibit the production of rheumatoid factor (RF) in rheumatoid arthritis (RA) patients," again citing the abstract. She further notes that "RA is an autoimmune disease and encompassed by the broader term, B-cell disorder." She concedes that "While all the antibodies 'under' the recitation, anti-MHC class II antibodies are not effective this does not preclude the teaching, anti-DR antibodies are effective in treating a B-cell disorder." Furthermore, she urges that "While a statement about anti-MHC class II in animals does not equate to a teaching of anti-DR in

animals, anti-Ia antibodies have been used successfully in animal models, see Brozek, bridging paragraph of columns 1 and 2 of page 105."

Previously the examiner relied upon an abstract of Brozek, citing a sentence saying that "Anti-MHC class II antibodies have been shown to have a profound effect on the immune system and have been used successfully in the therapy of human and animal autoimmune diseases." The examiner now provides the entire Brozek article, and it is clear that the previously cited statement from the abstract was referring to a statement in the background of the paper that "Exogenous anti-Ia antibodies have been used successfully for therapy in animal models of autoimmune diseases, including murine arthritis, lupus, encephalomyelitis, and myesthenia gravis, although the mechanisms involved in this therapy are not clear," citing the following articles:

16. Steinman, L., Rosenbaum, J. T., Sriram, S. and McDevitt, H. O. (1981). *In vivo* effects of antibodies to immune response gene products: Prevention of experimental allergic encephalitis. *Proc. Natl. Acad. Sci. U.S.A.*, 78, 7111.

17. Sriram, S. and Steinman, L. (1983). Anti I-A antibody suppresses active encephalomyelitis: treatment model for diseases linked to IR genes. *J. Exp. Med.*, 158, 1362.

18. Waldor, M. K., Sriram, S., McDevitt, H. O. and Steinman, L. (1983). In vivo therapy with monoclonal anti-I-A antibody suppresses immune responses to acetycholine receptor. *Proc. Natl. Acad. Sci. U.S.A.*, 80, 2713.

19. Adelman, N. E.,. Watling, D. L. and McDevitt, H. O. (1983). Treatment of (NZB x NZW) F 1 disease with anti-I-A monoclonal antibodies. *J. Exp. Med.*, 158, 1350.

20. Wooley, P. H., Luthra, H. S., Lafuse, W. P., Huse, A., Stuart, J. M. and David, C. S. (1985). Type II collagen-induced arthritis in mice. III. Suppression of arthritis by using monoclonal and polyclonal anti-Ia antisera. *J. Immunol.*, 134, 2366.

21. Broek, van den, M. F., Berg, van den, W. B. and Putte, van de, L. B. A. (1986). Monoclonal anti-Ia antibodies suppress the flare up reaction of antigen induced arthritis in mice. *Clin. Exp. Immunol.*, 66, 320.

22. Klinman, D. M., Lefkowitz, M. D., Raveche, E. S. and Steinberg, A. D. (1986). Effect of anti-Ia treatment on the production of anti-DNA antibody in NZB mice. *Eur. J.Immunol.*, 16, 939.

23. Vladutiu, A. O. and Steinman, L. (1987). Inhibition of experimental autoimmune thyroiditis in mice by anti-I-A antibodies. *Cell. Immunol.,* 109, 169.

24. Sriram, S., Topham, D. J. and Carroll, L. (1987). Haplotype-specific suppression of experimental allergic encephalomyelitis with anti-IA antibodies. *J.Immunol.*, 139, 1485.

However, all of the "therapy" in animals entails animal models of various diseases in mice, not domestic animals. The animal disease models include murine arthritis, lupus, encephalomyelitis, and myesthenia gravis. The cited documents deal with *experimental disease models*, not autoimmune actual diseases, and at least some of the titles indicate that the diseases, such as arthritis and allergic encephalomyelitis, *are induced as allergic response to an antigen such as collagen*. Hence they are not truly

indicative of results to be achieved in a true autoimmune disease. More particularly, results achieved in mice do not suggest that anti-HLA-DR antibodies would be useful in treating domestic animals, as presently claimed, and Brozek admits that "the mechanisms involved in this therapy are not clear." This, plus the fact that anti-Ia antibodies are not representative of all MHC-class II antibodies, or certainly anti-HLA-DR antibodies, means that the present invention would not have been obvious based on Brozek *et al.*

While no *prima facie* case of obviousness exists with respect to any of the pending claims, applicant now has amended the claims to recite treatment of lymphomas and leukemias in cats and dogs. According to the examiner, "all publications set forth treatment of B cell malignancies targeting the cancer antigens, see all documents in their entireties." This is certainly not the case. As noted by the examiner, "Halliwell teaches autoimmune diseases of domestic animals," and Brozek "teaches…treatment of autoimmune diseases." This is significant, in that the document relied upon as teaching the use the HLA-DR antibody (Brozek) does so ***only in the context of autoimmune disease***. Accordingly, there is no teaching in the record of using anti-HLA-DR antibodies to treat malignancies in animals and, more particularly, to treat leukemias and lymphomas in cats and dogs.

Forwarded with this response is a copy of an article submitted for publication relating to treatment of lymphoma in dogs. This article was only submitted in July, and therefore could not have been submitted prior to the final rejection. As such, its entry and consideration is believed proper at this stage of prosecution.

The article reports on an early study on the use of anti-HLA-DR monoclonal antibody in therapy for treatment of canine B-cell lymphoma. *In vitro* studies showed that murine L243 and its humanized IgG4 construct, IMMU-114, bind to normal and malignant canine lymphocytes and subsequently induce biological activity. *In vivo* studies indicated that the murine and humanized mAbs could be administered safely to dogs with lymphoma and bind to the malignant cells in nodal tissue. Preliminary evidence of disease stabilization was observed in dogs with advanced-stage lymphoma following anti-HLA-DR immunotherapy.

Dogs in this study had spontaneously-arising, and included dogs which had previously failed or were refractory to conventional cytotoxic chemotherapy. Although this study was not designed to evaluate true response probability, all dogs had tumor measurements and were evaluated for response. Two dogs with B-cell lymphoma that had received prednisone as their only prior therapy experienced measurable responses to L243. One experienced a minor, but measurable, response with significant improvement of advanced symptoms, while the second had a partial response lasting 8 weeks.

This response could not have been predicted based on Brozek in combination with the secondary references. The document relied upon as teaching the use the HLA-DR antibody (Brozek) does so ***only in the context of autoimmune disease***, and as to animals only in experimental disease models of autoimmune disease, in which the disease typically is induced by an allergen, *i.e.,* it is not an actual, spontaneous

autoimmune disease. The secondary references which disclose treatment of malignancies do so in humans. Accordingly, there is no teaching in the record of using anti-HLA-DR antibodies to treat malignancies in animals and, more particularly, to treat leukemias and lymphomas in cats and dogs, as presently claimed.

If there are any problems with this response, or if the examiner believes that a telephone interview would advance the prosecution of the present application, Applicant's attorney would appreciate a telephone call. In view of the foregoing, it is believed none of the references, taken singly or in combination, disclose the claimed invention. Accordingly, this application is believed to be in condition for allowance, the notice of which is respectfully requested.

Respectfully submitted,

ROSSI, KIMMS & McDOWELL LLP

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DATE

/BARBARA A. MCDOWELL/
BARBARA A. MCDOWELL
REG. NO. 31,640

20609 GORDON PARK SQUARE, SUITE 150
ASHBURN, VA 20147
703-726-6020 (PHONE)
703-726-6024 (FAX)